

REMARKS

Reconsideration of this application and entry of this amendment are requested. Claims 28-46 and 49-51 will be active in the application subsequent to entry of this amendment. The claims have been amended in order to more particularly point out and distinctly claim that which applicant regards as his invention. More specifically, claim 37 has been amended to be independent. In preparing this response claims 39 and 40 were found to be incomplete and they have been revised to include the wording in a similar manner to claim 38. Claims 47 and 48 have been rewritten as totally independent claims by incorporating the compound definition of claim 28 at the end of each; for convenience these now appear as new claims 49 and 50. In addition, claim 51 directed to a pharmaceutical composition has been added. It is not considered that the addition of a further claim will cause any undue burden at this juncture of the examination.

Applicants are pleased to note that claims 37, 39, 40, 47 and 48 are objected to as being dependent on a rejected base claim. In this response these claims have now been rewritten as fully independent claims, thus these claims are in condition for allowance.

There are remaining art-based rejections directed towards claims 28-36, 38 and 41-46, these claims being rejected as either anticipated by or "obvious" over the disclosures of U.S. 4,535,090 to Galliani et al.

Applicant is pleased to note that the examiner acknowledges the patentability of the compounds of formula (I) that are diphenyl-imidazole derivatives; and diphenyl-imidazole or diphenyl-triazole derivatives having a phosphorous or phosphate substituent

as well as the use of all compounds for treating tumors and/or immunological impairments.

According to applicant's understanding, the only compounds rejected by the examiner are diphenyl-triazole derivatives where R_5 is $-C(=O)-Z$ where $Z = OR_7$ and $R_7 = C_1-C_{10}$ aliphatic hydrocarbon (linear or branched). The examiner states that these compounds are the same as the compounds disclosed by Galliani et al or, to any extent they are not anticipated, they are obvious in view of Galliani et al (rejection - 35 USC 103). Applicant disagrees.

First, these compounds are not at all anticipated by Galliani according to 35 USC 102(b), as the compounds of the present invention which are rejected are **carbonates** (bearing an $-O-C(=O)-O$ -alkyl group) while Galliani's compounds are **esters** (bearing a $-O-C(=O)$ -alkyl group). While it is true that the two chemical entities are very close to each other, applicant cannot agree that it would be so obvious for the skill in the art to imagine the two entities show the same biological/pharmacological effect.

In fact, as clearly pointed out in the application (page 4, line 23 to page 5, line 7) Galliani's compounds (U.S. 4,535,090 being equivalent to EP 80053 which is quoted in the application) show severe species-specific variations in activity which render these compounds completely inactive in the higher mammal species, namely in human beings.

It is without question that the final aim of research in the biomedical/ pharmacological field is to find products for the human needs and definitely not for rats

As shown in Table 1 of the patent application and explained in the description related thereto, Galliani's compounds (A, B and C) show a hydrolysis rate of the ester group which is very slow in higher species, particularly in humans.

This fact is particularly important for two reasons:

- a. the true active ingredient of both types of compounds is the hydrolyzed derivative (i.e. the -OH derivative, not the ester nor the carbonate) as disclosed at page 16, lines 5-18 of applicant's specification, and
- b. the metabolic attack to the alkyl substituents on the phenyl radical other than the one bearing the carbonate or the ester (called R_1 in the instant invention and represented by a R_2 , R_3 -phenyl in Galliani's structure) leads to very poorly active metabolites as disclosed at page 18 lines 17-26 of applicant's specification.

It can therefore be easily understood that it is extremely important for the hydrolyzed active ingredient to reach its site of action before undergoing metabolic inactivation (see point b. above) and this is why it is essential that the release of the OH derivative be accomplished in a very short time.

As it can be seen from Table 1, the inventor found that the compounds of the invention show remarkably higher hydrolysis rates with respect to Galliani's compounds in dogs and especially in humans; as a consequence, when administered to a human being, Galliani's compounds will be metabolized to the inactive de-alkylated derivatives well before the true active principles can be released from the ester forms and as such reach their site of action. Thus Galliani's ester compounds could never be used as medicaments in humans as they would be completely inactive.

Unlike Galliani, the compounds of the present invention can be suitably used for the treatment of human beings due to their different behavior in the metabolic route they undergo after administration.

Based on the above, it will be apparent that, albeit their close chemical structure, the compounds of the invention show a noteworthy different effect compared to Galliani's products.

Contrary to Galliani's products that are far from being really active human medicaments, the compounds of the present invention can achieve their pharmacological effect thanks to their different chemical structure which allows them to exert their action before being inactivated by the metabolic route.

For the above reasons it is respectfully submitted that all of the claims in this application are in condition for allowance. Reconsideration and favorable action are solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page/s is/are captioned "**Version With Markings To Show Changes Made.**"

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Respectfully submitted,

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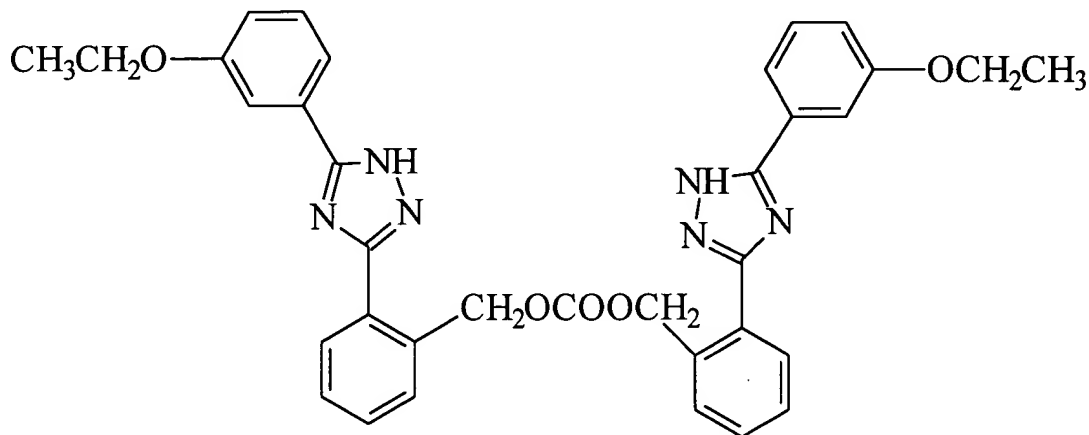
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

37. (Amended) Nitrogen heterocyclic aromatic derivative [according to claim 28]

having the following structure:



(XVII)

39. (Amended) The pharmaceutical composition comprising a nitrogen heterocyclic aromatic derivative according to claim 37 in the form of a transdermal skin patch.

40. (Amended) The pharmaceutical composition comprising a nitrogen heterocyclic aromatic derivative according to claim 37 for intravenous administration.